

## The changing epidemiology of inflammatory bowel diseases

A. Lapidus

Department of Gastroenterology, Ersta Hospital, Stockholm, Sweden.

### Abstract

Epidemiological studies of inflammatory bowel disease are important in order to find possible clues to the still unknown etiology, as well as for the planning of the health service. In supplement to short-term studies, reporting the actual state of the disease, long-term studies are requisited to follow up the development of inflammatory bowel disease.

Inflammatory bowel disease has become more frequent during the past decades, with an approximate prevalence of 0.5% in the northern part of the world. A changed disease panorama can be noted with increasing median age at diagnosis, a growing entity of patients with colorectal Crohn's disease and a shift towards more distal ulcerative colitis. The increased age at diagnosis is attributed to a postponement of the age-specific incidence peak. While the difference between gender has levelled off, difference still exists in young adults in Crohn's disease and in elderly in ulcerative colitis. *Colorectal cancer has become a matter also in Crohn's disease.* (Acta gastroenterol. belg., 2001, 64, 155-159).

Crohn's disease and ulcerative colitis are the two major inflammatory bowel diseases (IBD).

Crohn's disease may affect any part of the gastrointestinal tract, in contrast to ulcerative colitis, which only involves the colon and rectum. The etiology and pathogenesis of the inflammatory bowel diseases still remain obscure.

Medical history includes evidence for the existence of Crohn's disease as well as ulcerative colitis. In 1859 Sir Samuel Wilks used the term "ulcerative colitis" in describing the post-mortem findings of a young woman dying after three weeks of illness (1). The autopsy showed peritonitis due to inflammation in the terminal ileum and ulcers of various sizes in the entire colon, most markedly in its proximal part. This description, however, seems to be more typical for Crohn's disease. The difficulty to separate the two entities is still a matter of concern and about 10% of the cases with inflammatory disease confined to the colon are classified as indeterminate colitis (2).

Bringing matters to a head, the concept of Crohn's disease is a rather rare disease mostly localised to the ileocaecal area, occurring in young adults, preferably smoking women liable of Jewish birth, living in an urban area in the northern part of the world. Ulcerative colitis is associated with non- or ex-smoking males and the risk of developing colorectal cancer is evident. But, will these stereotyped descriptions be applicable in the twenty-first century?

Following reports of sporadic cases of inflammatory bowel diseases, Acheson and Evans performed the first

epidemiological studies of Crohn's disease and ulcerative colitis in the 1960s (3). Several studies have been published since then. Some centers had the possibility to carry out long-term studies and found a rather unaffected incidence of ulcerative colitis over time since the 1960s (4,5). However, studies from Sweden showed a further increase of the incidence of ulcerative colitis during the seventies (6-8). An average annual incidence increase of 5% from 4.2 to 9.4 new cases per 100,000 inhabitants, of definite ulcerative colitis was found in Malmö between 1958 and 1982. In Örebro, the incidence of ulcerative colitis increased from 3.3 to 15.0 per 100,000 between 1963 and 1982, but decreased subsequently to 11.2 between 1983 and 1987. Furthermore, in Copenhagen, there were significant increases in incidence of ulcerative colitis in the early 1970s and in the early 1980s, both of which were, however, followed by significant decreases (9).

On the contrary, time trends in Crohn's disease seem to have been more consistent with a gradual increase of incidence during the 1960s and 1970s (6,10-13). Thereafter most studies show a plateau (6,12,14,15) or a slight increase in the incidence rate during the late 1970s and 1980s (11,13,16,17). Some studies have indicated a more substantial increase through the 1980s (18).

The development of inflammatory bowel disease on Iceland has been studied retrospectively between 1950 and 1989 (19) and prospectively between 1990 and 1994 (20). The 45 year long study period revealed a steady increase of incidence of ulcerative colitis as well as of Crohn's disease. The mean annual incidence rose from 7.4 to 16.5/100,000 and 0.9 to 5.5/100,000 respectively between the 1970s and 1990s.

In summary, inflammatory bowel diseases have become more frequent during the second half of this century. The incidence of ulcerative colitis has levelled off while there is evidence of a continuous increase of Crohn's disease during the eighties. We are now looking forward to a further follow-up of these long-term studies, to conclude whether the trends are also applicable for the 1990s.

There are obvious differences in incidence rates of inflammatory bowel disease around the world and even some variations between areas close to each other and within the same country (21-24).

Corresponding author: Lapidus A., Department of Gastroenterology, K63, Huddinge University Hospital, Huddinge 14186, Sweden.

Several possible biases should be taken into account when comparing data from different areas as well as over time. A well-defined study area and population, and an organised health-care system, are prerequisites for incidence studies.

Case identification may influence the incidence rates. Most series have been hospital based and only a few series have also included out-patients. Patients having a subclinical or mild form of disease may therefore be overlooked, resulting in a too low incidence rate. Furthermore, the study designs may vary according to inclusion criteria i.e. definite and probable cases of inflammatory bowel disease and whether the study is of a retrospective or prospective character. Finally, the incidence is generally based on the date of diagnosis — rather than the time of onset for the first symptoms — of inflammatory disease. Different diagnostic procedures and accuracy may alter the time span between symptoms and diagnosis during a long study period. A long period between the appearance of symptoms and the time of diagnosis may therefore postpone the true incidence.

In order to avoid these pitfalls, the European collaborative study on inflammatory disease, including 20 European centres, was conducted between 1991 and 1993 (25). A north-south gradient was confirmed, although the difference in incidence rates was less pronounced than previously assumed. The rates of ulcerative colitis in northern centres were 40% higher than those in the south (11.8 vs 7.0), with the highest incidence found in Iceland and lowest incidence in southern Portugal. The incidence of Crohn's disease was 80% higher in the north compared with the south (7.0 vs 3.9). The lowest incidence was found in Ioannina in Greece, although the incidence of Crohn's disease in Heraklion, Crete was fourfold at the same time.

There is some ethnic and racial variation in inflammatory bowel disease. Inflammatory bowel disease has been reported to be less occurring in black populations than white (26,27). In opposite, the Jewish population is more prone to develop inflammatory bowel disease than other ethnic groups (28). In Israel, Ashkenazi Jews have a higher incidence than Sephardi Jews, but a lower incidence than Ashkenazi Jews in the United States or Northern Europe (29). Thus, there may be a genetic predisposition (30), nevertheless environmental factors should also be considered in the etiology of inflammatory bowel disease. A more recent study, however, found a similar prevalence of Crohn's disease in both types of Israeli Jews (31).

Although the incidence of inflammatory bowel disease is low in Asia, people of Asian origin in UK have a high incidence of ulcerative colitis (32). A longitudinal birth cohort study revealed that Asians born in Britain were significantly more likely than indigenous Europeans to have a diagnosis of IBD (33). Few studies have been reported from developing countries, due to absence of reliable demographic data, but a recent paper from

India reported on 25 patients with CD and concluded that CD may not be rare in India (34). A high prevalence of infectious gastrointestinal disorders in these countries may also mask the true incidence of ulcerative colitis and Crohn's disease.

Inflammatory bowel disease can present itself at any time in life but occurs mostly in young adults. The highest age-specific incidence is found among persons aged between 15 and 30 years (35). Ulcerative colitis mostly presents at a slightly higher age than Crohn's disease (6). A second peak of incidence among elderly has also been reported (5,18,36).

The median age at diagnosis has increased overtime, in both ulcerative colitis and Crohn's disease (6,13,14). The increased median age at diagnosis is partly attributed to an increased proportion of elderly (i.e. > 65 years at diagnosis) patients (14). In ulcerative colitis, an increased incidence has particularly been seen in elderly men (4,9,21,25,37). However, the major reason for the increased age at diagnosis seen in inflammatory bowel disease over time is probably a five-year postponement of the age-specific incidence-peak (6,14).

Generally, Crohn's disease has been considered to affect women more than men (11,13,16,38) but several studies have demonstrated no difference between gender (12,25,29).

A changed pattern in gender over time has been observed in ulcerative colitis. By scrutinising 56 previous studies with reference to gender, the ratio man/woman among patients diagnosed between 1930 and 1990 was found to increase from 0.5 to 1.3 (40). Thus, ulcerative colitis seems to be most common among men; still some studies have reported an equal incidence in men and women.

In the European collaborative study on inflammatory bowel disease, the incidence of ulcerative colitis in the 25-34 year age-specific group was similar in both sexes (25). However, with increasing age, the age-specific incidence in men remained high, in contrast to women in whom the age-specific incidence decreased.

In Crohn's disease, in contrast to ulcerative colitis, a decreasing age-specific incidence was found with increasing age in both sex and no second peak was apparent in the elderly. The incidence among women was higher than in men in the 15-34 age-specific groups, but equal in patients aged > 34 years at diagnosis.

Nevertheless, an increasing median age at diagnosis, data suggest that inflammatory bowel disease in children has increased overtime. In Stockholm, the incidence of Crohn's disease among children (< 17 years) was recently reported to have doubled from 2.4 to 5.5/100,000 between 1990-1992 and 1996-1998 (41). These figures could, however, not be confirmed in a larger Swedish study, including 57% of the paediatric population (42). That study showed an overall increased incidence rate of inflammatory bowel disease in children, 15 years of age or less, from 4.6 to 7.0/100,000 between 1984 and 1995

but the increase was made up by an increase of ulcerative colitis and not of Crohn's disease. Different age criteria, as well as a possible reduced time between onset of symptoms and diagnosis must be taken into account when comparing these studies.

Ulcerative colitis is generally classified as proctitis, left-sided, extensive or total colitis, but the definition of extent of disease varies between studies. The overall proportion of total colitis is rather consistent between studies with an approximately rate of 20-30% (5,6,7,9). Extensive and total ulcerative colitis seem to be most frequent in young adults (6,9), but has also been noted in elderly men (21). The incidence of total ulcerative colitis has been stable or decreasing during the 1980s (5,7,9), except for a further increase in men reported from Minnesota in USA, during the late eighties and early nineties (4).

On the contrary, the figures for ulcerative proctitis differ between studies, with a range from 22% to 59% (7,8). Most longitudinal follow-up studies have shown an increasing incidence particularly of ulcerative proctitis, but also of left-sided ulcerative colitis overtime (6-8). No difference in extent of disease has been found between northern and southern situated countries (25).

In the original report by Crohn *et al.* (43), Crohn's disease was considered to affect the small bowel and particularly the terminal ileum. It was not until 1960 that Crohn's disease localised to the colon/and rectum was regarded as an entity of its own, unrelated to ulcerative colitis (44). Classical ileocaecal Crohn's disease has been the most common disease localisation followed by ileocolonic and colorectal disease. Crohn's disease lesions in the gastro-duodenal region are rare and mostly associated with inflammation elsewhere in the gastrointestinal tract.

Again, the definition of extent of disease varies between studies. Colorectal disease has been rather uniformly classified while the ileocaecal area has been classified to either small bowel disease or to ileocolonic disease.

An increasing proportion of colorectal disease over time has been found in several studies (17,18,20,36). Still, some investigators have reported an unaltered pattern (13), and one study even showed a slight decrease in colorectal disease (12). In Stockholm County the proportion of colorectal disease doubled from 15% to 32% between 1955-64 and 1980-89, while the proportion of ileocaecal Crohn's disease decreased from 58% to 41% during the same time period (14). A recent update of Crohn's disease in Cardiff supported this trend, by reporting a continuous increase of colorectal disease notwithstanding an overall stable incidence (38). The increased proportion of colorectal disease in Stockholm was not attributed to an increasing number of elderly over time, the proportion of colorectal disease being similar in elderly and young patients. Left-sided colorectal Crohn's disease tended however, to be more common in elderly than in younger patients (45). In

contrast, young patients (aged < 30 years at diagnosis) more often had total colonic disease compared to the rest of the patients.

A higher incidence of inflammatory bowel disease has been seen in urban populations compared to rural populations (46). In Minnesota the incidences of Crohn's disease and ulcerative colitis were 40%-146% higher in urban counties compared with rural counties (15). Similar data were reported from Uppsala (6), where the difference between urban and rural counties remained unchanged over time. However, there are conflicting data, and the differences may theoretically be due to less access to health care in the rural areas. Nevertheless there may be a real difference due to living conditions, including smoking habits.

An association between ulcerative colitis and gastrointestinal cancer was already reported in 1928 (47). Early studies showing a 40% risk of developing colorectal cancer in long-standing total ulcerative colitis, advocated prophylactic proctocolectomy. Later performed population-based studies reported a considerably lower risk of developing colorectal cancer and the prophylactic proctocolectomies were abandoned for surveillance programs. The risk of developing colorectal cancer in total ulcerative colitis increases at 8 years from onset of disease and is markedly increased at 20 years after onset of disease compared to the general population (48). The cumulative risk of colorectal cancer at 20 years disease duration has been estimated between 1,8% and 24% in different studies (48-51). There are indications that the risk may have decreased over time, partly due to anti-inflammatory treatment (52). A cohort study of 1161 Danish patients with ulcerative colitis did not find any increased risk for colorectal cancer. The calculated lifetime risk for developing colorectal cancer was 3.5% for patients with ulcerative colitis compared with 3.7% for the Danish population (50).

In Crohn's disease, the whole gastrointestinal tract must be considered regarding cancer, in contrast to ulcerative colitis where only the colon/rectum is affected. Some population-based studies have reported an increased risk of small bowel carcinoma in patients with Crohn's disease compared with the general population (53,54) and several studies from referral centres are in accordance. Still the number of patients developing small bowel carcinoma is low.

Data on the occurrence of colorectal cancer in Crohn's disease are inconsistent. A population-based study from Uppsala in Sweden (55) including 1655 patients, showed an increased risk of 3.2 respectively 5.6 for ileocolonic and colorectal Crohn's disease. Patients in whom colonic Crohn's disease was diagnosed before the age of 30 years run a higher risk than those diagnosed at older ages (RR = 20.9 vs. 2.2). Similar results were reported from Great Britain, where patients with extensive Crohn's colitis showed an 18-fold increased risk of developing colonic cancer, which decreased with increasing age at onset (56). In contrast,

no increased risk of developing colorectal cancer could be established either in studies (53,54) performed in Copenhagen nor in Stockholm.

To sum up, with approximately 0,5% of the northern situated population suffering from inflammatory bowel diseases, and an increasing incidence in former "low-incidence" areas, we can conclude that inflammatory bowel diseases have become rather common. Ethnic variations and difference between gender are blurred out. Still, differences in gender exist in young adults in Crohn's disease and in elderly in ulcerative colitis. Although the mean age at diagnosis has increased over time, children with inflammatory bowel disease is a growing entity. The pattern of disease localisation has changed; distal ulcerative colitis and proctitis have become more common, and in Crohn's disease there is an increasing proportion of patients with only colorectal disease at the expense of decreasing classical ileocaecal Crohn's disease. Colorectal cancer has become a matter also in Crohn's disease whereas the risk of colorectal cancer in ulcerative colitis may have decreased.

Despite an unknown etiology, the changed epidemiology of inflammatory bowel diseases seen over time may be attributed to environmental factors including altered smoking habits. A few longitudinal studies have been performed during the early 1990s, yet it is essential to continuously follow up of the development of inflammatory bowel disease in order to find a possible clue to the etiology as well as to plan the health care.

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